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The promise of self-assembled 3D supramolecular coordination complexes for biomedical applications

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Abstract

In the supramolecular chemistry field, coordination-driven self-assembly has provided the basis for tremendous growth across many sub-disciplines, spanning fundamental investigations regarding the design and synthesis of new architectures to defining different practical applications. Within this framework, supramolecular coordination complexes (SCCs), defined as large chemical entities formed from smaller precursor building blocks of ionic metal nodes and organic multi-dentate ligands, resulting in intricate and well-defined supramolecular structures, hold great promise. Notably, interests in the construction of discrete 3D molecular architectures, as those offered by SCCs, have experienced extraordinary progress due to their potential application as sensors, catalysts, probes, containers and in basic host–guest chemistry. Despite the numerous synthetic efforts, and a number of inherent favourable properties, the field of 3D SCCs for biomedical applications is still in its infancy. This Viewpoint focuses on 3D SCCs - specifically metallacages and helicates - first briefly presenting the fundamentals in terms of synthesis and characterisation of their host-guest properties, followed by an overview of the possible biological applications with representative examples. Thus, emphasis will be particularly given to metallacages as drug delivery systems, and to chiral helicates as DNA recognition domains. Overall, we will provide an update on the state-of-the-art literature and will define the challenges in this fascinating research area at the interface of different disciplines.

1. Introduction

Over the last few decades, the area of metallosupramolecular chemistry has grown exponentially. Usually, the coordination compounds for this type of chemistry are classified into two main branches: metal-organic frameworks (MOFs) and supramolecular coordination complexes (SCCs). MOFs are metal-organic porous coordination

polymers consisting of metal ions or clusters and organic linkers, which are connected by metal–ligand coordination bonds.¹ Instead, SCCs are well-defined, discrete 2D or 3D molecular entities with suitable metal centres undergoing coordination-driven self-assembly with ligands containing multiple binding sites.² Through the judicious choice of the coordination geometry of the metal ion precursor and complementary structure of the multidentate ligand, an almost infinite range of MOFs and SCCs can form *via* the process of self-assembly.^{3,4} Over the years, several strategies have been used to design these systems, including directional bonding, symmetry interaction, insertion of non-coordinating templates, molecular panelling, reticular chemistry etc.²

The host-guest properties of supramolecular complexes are certainly one of their key features, making them not only aesthetically pleasing architectures, but also attractive for a wide range of potential applications in catalysis,⁵ fluorescent probes design,⁶ and in the development of novel theranostics and therapeutics.⁷ For example, in the case of MOFs, their rigid morphologies and tuneable pore sizes have been exploited in catalysis,^{8,9} taking advantage of the enhanced surface area used as a support structure for the active catalytic substance, while the pores can be altered to filter specific molecules for a certain reaction. Other promising applications of MOFs undergoing investigation are in molecular separation¹⁰ and drug delivery.¹¹ In the context of SCCs, 2D metallacycles, formed from cationic metal nodes with two available coordination sites and bidentate Lewis base ligands, started to be reported during the late 80's and into the 90's.^{12,13} Initial interest for these 2D structures relied mainly on their aesthetically pleasing symmetry, however applications in catalysis¹⁴ and molecular recognition have since been reported,¹⁵ including as selective sensors for biologically important analytes.¹⁶

Still within the SCCs family, 3D cage-like structures - also defined as metallacages - are of great interest, as their geometry generally allows an internal cavity to encapsulate guest molecules. Metallacages of the general formula $M_xL_y(L'_z)$ (M: Metal; L, L': Ligands) form a highly diverse class of structures due to the interchangeable nature of both ligand and metallic nodes. An essential role in determining the resulting metallacage structure (geometry and size) and chemical properties is played by the metal ion, which is commonly a transition metal (*i.e.* Fe(II), Co(II), Ni(II), Cu(II), Zn(II), Mo(II), Ru(II), Rh(II), Pd(II) and Pt(II) ions have been used) or a lanthanide. Overall, the combination of the coordination geometry of the selected metal ion with different ligands can give rise to a great variety of supramolecular scaffolds for different applications.¹⁷ Recently, numerous thematic reviews have discussed the vast progress in the design and synthesis of these attractive materials.^{2,18–21} Thus, our Viewpoint is not intended to present the design perspective in detail, rather to summarize some general design principles focusing on the most recent examples from those cage systems having biomedical implications. In fact, while in the last 10 years there has been an exponential growth of the number of papers related to the synthesis of SCCs, although always reduced compared to MOFs, the reported studies including their biological/biomedical applications are still limited (Figure 1).

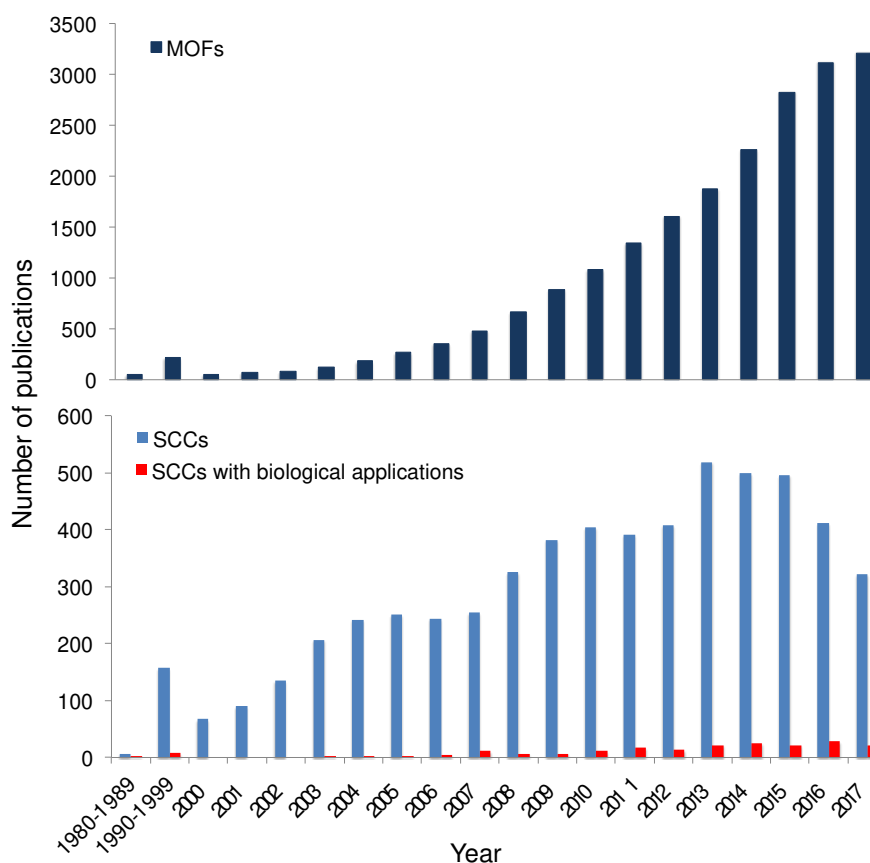


Figure 1. Graph showing the evolution of the number of publications per year since 1980 regarding MOFs (top), SCCs and SCCs with biological applications (bottom) (Source: Scopus, last accessed 8th November 2017).

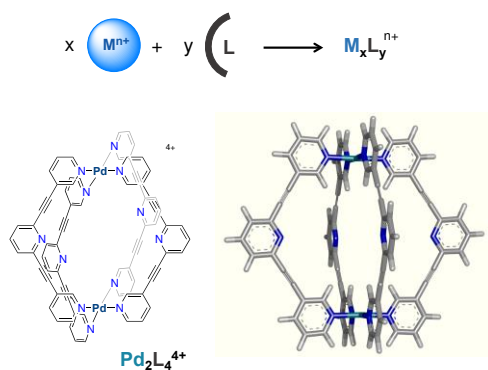
There are numerous methods to categorise 3D SCCs, such as the resulting cage geometry, the ratio of ligands to metals, the type of self-assembly or by the metal ion used. For the purpose of this Viewpoint, we will mainly focus on metallacages and helicates, highlighting the state-of-the-art research towards their biological applications, including as drug delivery systems and for DNA recognition with potential applications in imaging and therapy. Overall, we aim at providing the future outlook for this exciting research field, which, in defining the various challenges, will hopefully stimulate new ideas within the bioinorganic and medicinal inorganic chemistry community.

2. Metallacages and helicates: general principles

The synthesis of metallacages has recently been the topic of several reviews,^{22–24} and has been shown to be extremely predictable with the careful choice of complementary ligands to metal, and in most cases proceeds under mild conditions *via* self-assembly to produce quantitative yields of the desired complex. Specifically, metallacages can be formed *via* two self-assembly methods, namely *edge directed* *via* direct coordination of the ligands to the metal ions, resulting in the general formula M_xL_y (Figure 2A), or *face directed* synthesis (Figure 2B). The latter

consists of altering the available coordination sites of the metal ion to impose a degree of directionality with an appropriate ligand to form a precursor coordination complex. Upon introduction of complementary and multidentate ligands, the desired metallacage will form *via* self-assembly with the general formula $(M_xL')_zL_y$ (Figure 2B). As an important requisite for the polyhedral structure, at least one component of the systems must show a bent geometry (with a bending angle $\theta < 180^\circ$). This provides the needed curvature for the formation of a finite symmetry. Such cages are, therefore, assembled from rigid, planar multidentate ligands covering the face of the resulting capsules geometric face. For example, in 2004 Oppel-Müller *et al.* have reported the first Pd(II) closed coordination capsule with octahedral outer shape predicted to be able to encapsulate at least four water coordinated sodium ions.²⁵ Moreover, Fujita *et al.* have reported a $(Pd_6(1,2\text{-diamineethane}))_6L_4$ cage from the self-assembly of planar tridentate ligands and *cis*-capped Pd^{2+} ions at a 4:6 ligand:metal ratio, with a resulting geometric structure of an octahedron with four of the eight faces covered by the tridentate ligand (Figure 2B).²⁶

A. Edge-directed metallacages



B. Face-directed metallacages

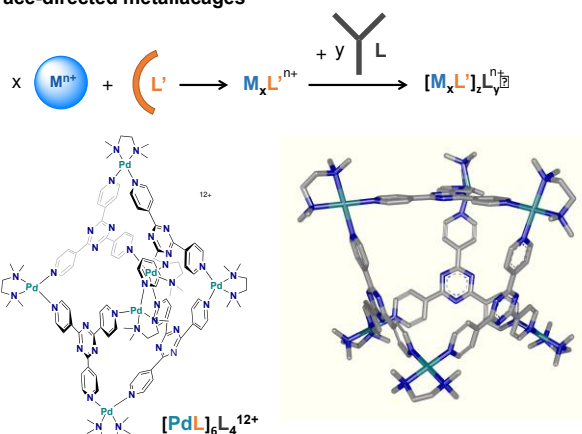


Figure 2. Representative synthetic schemes, structures and examples of **A.** One step self-assembly of $M_xL_y^{n+}$ edge-directed metallacages, as described by Crowley *et al.*²⁷ **B.** Two-step self-assembly of $[M_xL']_zL_y^{n+}$ face-directed metallacages, as described by Fujita *et al.*²⁶ Structures were obtained from CCDC (n° 853226 and 293777) and modified accordingly using Discovery Studio software.

Furthermore, Fujita *et al.* have reported the synthesis of a series of $Pd_{12}L_{24}$ and $Pd_{24}L_{48}$ *edge directed* type metallacages, where the selected ligands are structurally similar five membered heterocycles functionalised with two pyridine “arms” (Figure 3).²⁸ The cages were characterized using 1H NMR and CSI-MS (Cold-Spray Ionization Mass Spectrometry). Notably, by changing the element or position of the heteroatom in the central five membered heterocycle, it was possible to fine-tune the angle between the two coordinating pyridine “arms” of the ligand and determine this angle by DFT calculations. The results showed that, when the bond angle was between 134° and 149° , $Pd_{24}L_{48}$ cages were formed, whereas a bond angle between 127° and 131° favoured exclusively the formation of $Pd_{12}L_{24}$ cages (Figure 3).²⁸ It was suggested that the switch of formation between a $Pd_{12}L_{24}$ cage and a $Pd_{24}L_{48}$ cage must lie between the range of 131° - 134° , although it was noted that a mixture of the two cages was never observed.

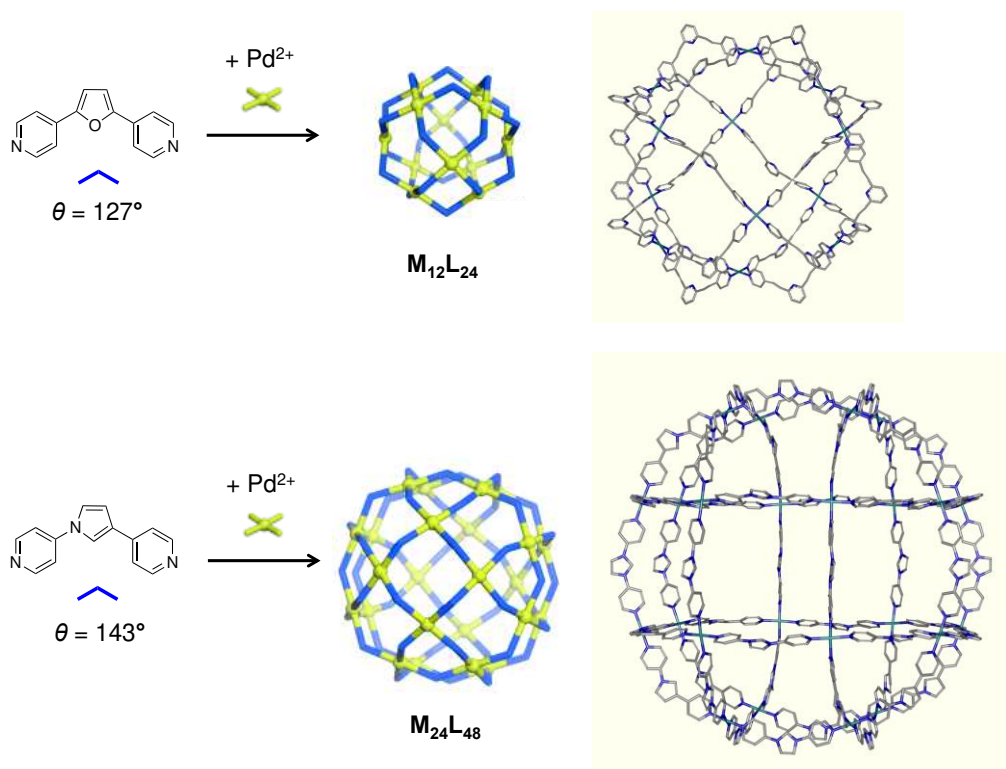


Figure 3. Structures of $\text{M}_{12}\text{L}_{24}$ and $\text{M}_{24}\text{L}_{48}$ types of metallacages described by Fujita *et al.*²⁸ The X-ray structures were obtained from CCDC (n° 927643 and 860617) and modified accordingly using Discovery Studio software.

Interesting, Raymond and coworkers have reported an example of both *edge* (M_4L_6) and *face* (M_4L_4) directed Ga-based tetrahedral metallacages.²⁹ The interactions between both type of metallacage host structures and a range of guest molecules have been explored,^{29–32} and the *edge* directed M_4L_6 cages were found to exhibit a greater scope of host-guest chemistry compared to the *face* directed M_4L_4 .^{29,30} It was hypothesised that the broader range of host-guest chemistry of the M_4L_6 type architecture could be attributed to the increased flexibility of the *edge* directed scaffold. This flexibility allows slight conformational changes of the host cage favoring stronger association with the guest molecule, similarly to what is observed for highly specific protein-ligand interactions in biological systems.

The controlled synthesis of heteroleptic cages would be extremely attractive for biological applications as, unlike homoleptic cages, more than one type of ligand, featuring different functional groups (*e.g.* to achieve both imaging and targeted therapeutic effects), could be used to form the SCC. Most polyhedral complexes reported to date contain only one type of ligand, and this results in a simple single product. Self-assembly involving two or more different ligands has often been examined with the aim of generating more elaborate structures and functions, but a clear strategy to predict and account for the structures of mixed-ligand self-assembly does not seem to exist.³³ Although the synthesis of heteroleptic cages has been reported, the only examples to date, achieving an isolated product with a vacant internal cavity, are inherently those that follow the *face directed* synthesis, whereby a tightly

bound organometallic precursor is first synthesised, followed by the self-assembly of the metallacage upon introduction of a multidentate Lewis basic ligand. However recently, there have been reports of the synthesis of multicomponent, heteroleptic *edge directed* metallacages.^{34–37} Unfortunately, the examples reported so far do not isolate a single, pure heteroleptic cage but rather a mixture of multicomponent cages.³⁸ For example, Crowley *et al.* have described the controlled synthesis of heteroleptic metallacages of the general formula $\text{Pd}_2(\text{L}_a)_2(\text{L}_b)_2$ using structurally similar tripyridyl ligands, which was discovered while carrying out competitive ligand substitution experiments (Figure 4).³⁹ The study showed that the addition of an amino functional group to the terminal pyridine of the ligand would replace the original tripyridyl ligands due to the electron donating properties of the amino substituent. Interestingly, when the amino group was functionalised in the *ortho* position of the terminal pyridine ring, a stable heteroleptic cage was formed. DFT calculations were carried out on the new cage product and determined that the *cis*- conformation was energetically more favourable than the *trans*-. Furthermore, large downfield shifts for the amino protons in the ^1H NMR spectra of the heteroleptic cage were observed, attributable to hydrogen bonding between the adjacent amino groups, as well as further hydrogen bonding to the acidic α -H of the adjacent tripyridyl ligands.

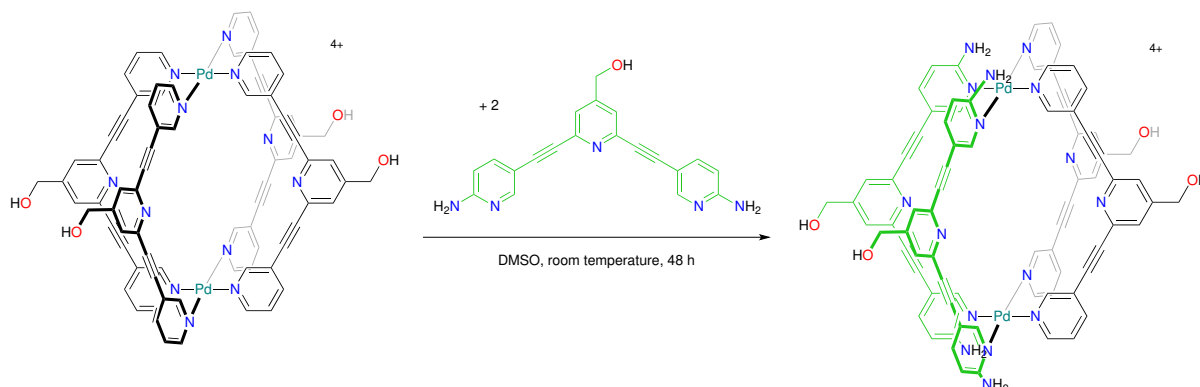


Figure 4. Example of an heteroleptic cage of the type $\text{M}_x\text{L}_y\text{L}'_z{}^{n+}$ formed by ligand exchange, as described by Crowley *et al.*³⁹ The *cis*- isomer was found to be more stable than the *trans*-.

Within the 3D SCCs, helicates typically consist of ligands formed from a binding unit and a spacer unit (Figure 5A), with coordinated metal ions to ensure the structure integrity. The term helicate was first introduced by Lehn *et al.* in 1987 to describe both a di- and tri-nuclear self-assembled, helical structure of $\text{Cu}(\text{I})$ ions with ligands composed of two and three linked bipyridine molecules, respectively.⁴⁰ The crystal structure was determined for the tri-nuclear helicate and revealed a 1:1 ratio of helicates with opposite chirality. It was predicted that introducing ordered functional groups into this basic scaffold could be exploited for biologically relevant applications. As such, many helicates cannot be literally described as cage-complexes as they lack vacant internal pores to accommodate guest molecules. Over the following decade, numerous reports showed examples of double and triple stranded helicate structures using different metal ions and ligands, well described by a comprehensive review by Hopfgartner *et al.*⁴¹ The diverse morphologies of these chiral structures have continued to appeal to synthetic chemists since

then and more examples of helicates have been reported, although optically pure helicates are much rarer.⁴² Several kinds of inert metal helicates maintain rigid helical structures and their stereoisomers are separable by optical resolution techniques, while labile metal helicates offer dynamic inversion of their helical structures – ‘chirality switching’ - *via* non-covalent interactions with external chemical signals.⁴³ The latter could be exploited as time-programmable switches of chirality-derived dynamic rotations, translations, stretching and shape flipping, for diverse applications in nanoscience and related technology.

Interestingly, helical structures that can accommodate guest molecules have been recently reported.^{44,45} For example, Kruger *et al.* have synthesized a triple stranded Fe(II) helicate structure that was hypothesized to accommodate up to two chloride ions within two vacant internal pores.⁴⁶ The structure of the host-guest system was studied by ¹H NMR titration experiments, revealing that, upon addition of Cl⁻ ions, a significant downfield shift of the signals of both the amide and bipyridyl protons occurred, indicative of hydrogen bonding. The titration experiments also showed a 1:2 host to guest stoichiometry. This result, along with the observation that the triple stranded *rac*-isomer was favoured over the *meso*-isomer, led to propose that the Cl⁻ ions occupied the helicates internal cavity, and improved the chirality nature by giving structure *via* hydrogen bonding. Most reported cases of helicate host-guest complexes provide evidence for encapsulation of anions into the vacant helicate cavity; however, at the time of writing, no instances of host-guest helicate complexes could be found that took advantage of helicates chiral nature by preferentially encapsulating one enantiomer over another. Interestingly, Cui *et al.* have reported quadruple stranded helicates that, in the solid state, provided a certain degree of enantioselectivity when introduced to a racemic mixture of small chiral molecules (Figure 5B).⁴² However, the degree of separation was not large enough to yield an enantiopure product.

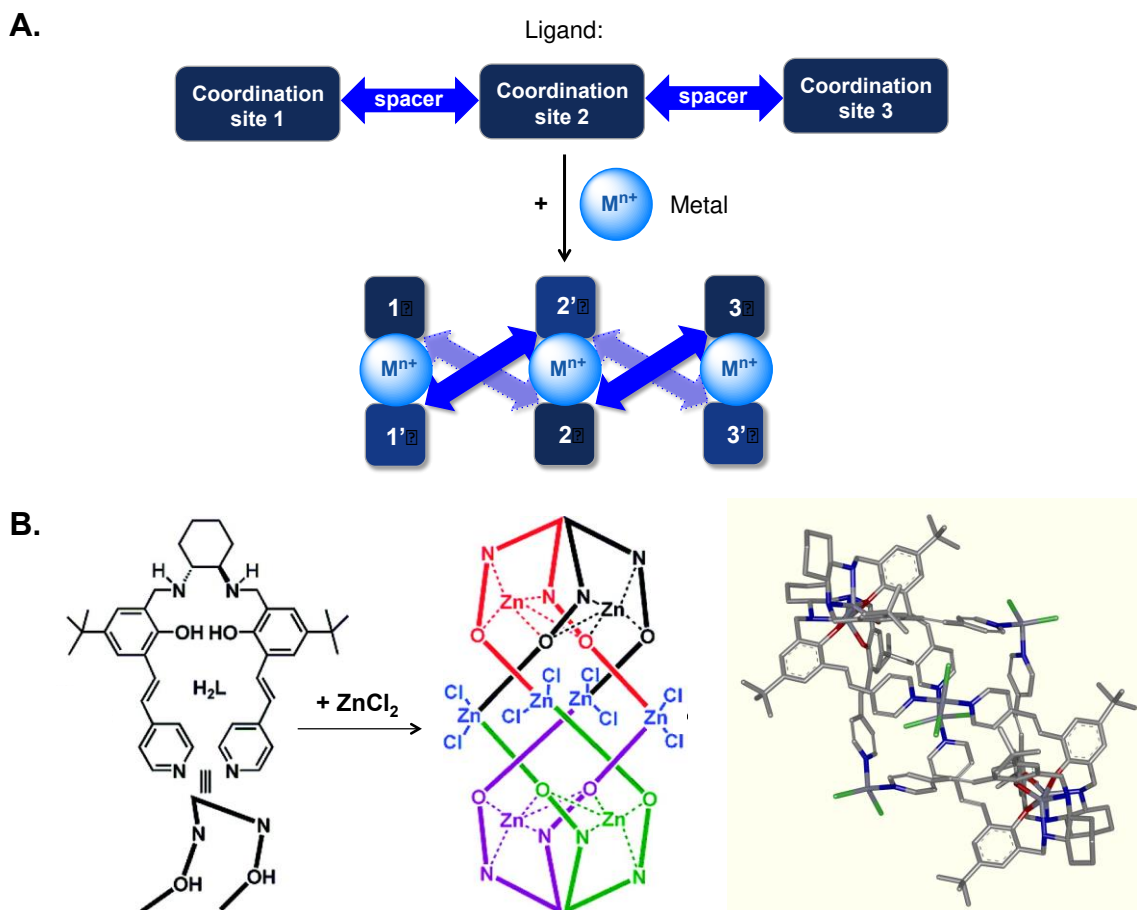


Figure 5. A. Representative scheme of the synthesis of helicates; **B.** Example of a helicate structure taken from reference⁴². The X-Ray structure was obtained from CCDC (n° 857191) and depicted using Discovery Studio software.

3. Metallacages as Drug Delivery Systems

In the last decade, the number of reports on the anticancer activity of 3D SCCs with different shapes (helicates,^{47,48} cages,⁴⁹ rectangles, boxes,^{50–52} prisms^{53,54} and capsules⁵⁵) and different compositions (M_2L_3 , M_2L_4 , M_4L_4 , $M_4L_2L'_2$, $M_6L_6L'_2$, $M_8L_8L'_2$), where M is usually Fe(II), Pd(II), Pt(II), or half-sandwich organometallic clips based on Ru(II), Os(II), or Ir(III) and Rh(III), has increased exponentially. The characteristic advantages of the SCCs, over small bioactive metal complexes, are their larger size (usually of 1 to 10 nm) and well-defined structure and cavity, which can improve their therapeutic profiles through combined effects or alternative mechanisms of action.

In this Viewpoint, we decided to focus on the systems that showed promise for biomedical applications not due to their intrinsic anticancer potential, but for their favourable properties as drug delivery systems. This is particularly relevant to cancer chemotherapy, whose success rate remains limited, primarily due to scarce selectivity of drugs for the tumour tissue, often resulting in severe toxicity and in the development of drug resistance. In fact, different strategies to achieve drug targeting, such as tethering anticancer compounds to or encapsulating

them in a wide range of functional molecules or nanomaterials (with or without active targeting groups), have been developed.^{56–58} For example, lipid nano-systems, such as liposomes and micelles along with virus-inspired vectors and polymeric particles, as well as inorganic nanoparticles, have been studied to deliver bioactive compounds to tumour sites. However, such targeted constructs have several limitations: for example, polymers and dendrimers often require considerable synthetic effort and can be plagued by low yields and largely amorphous final structures, while nanoparticles often present issues of toxicity and lack of biodegradability.⁵⁹

In general, encapsulation of a drug molecule within an internal cavity of a soluble host structure may protect the compound from the harsh physiological conditions, as well as increase the solubility of lipophilic molecules. Furthermore, conjugation of molecules such as targeting moieties or fluorophores to the outer surface of the host complex may provide further desirable properties to the host-guest complex without affecting the structure of the drug molecule. In this context, supramolecular metallacages offer several properties that make them attractive candidates for future drug delivery systems. For example, the rigid, porous structure offers a secure cavity for small drug molecules and the ability to modify the ligand structure both pre- and post-synthesis allows for the properties of the resulting structure to be improved. Furthermore, since metallacages, at variance with MOFs, are discrete chemical entities, the issues of solubility in aqueous environment can be potentially overcome. Despite their ideal features, currently the full potential of metallacages as drug delivery vehicles has not been realised, with most publications focusing on the synthesis and characterisation of these novel structures and only suggesting what future applications may be. The lack of substantial research into biological applications for this type of SCCs may stem from some unattractive properties often associated with metal complexes, such as instability in aqueous environment and toxicity concerns of both the ligand and metal ions components. Moreover, the control of their host-guest properties in the complex biological medium needs to be demonstrated. To this aim, the development of suitable methods to study the encapsulation and drug release properties of metallacages in physiological conditions (i.e. at micromolar concentration, in the presence of buffer components, etc.) is essential.

This specific research area has been pioneered by Therrien *et al.*, who were the first to report in 2008 on the self-assembly of hexaruthenium metallacages (metalla-prisms),⁶⁰ based on previous studies on ruthenium(II) metallacycles developed by Süss-Fink *et al.*,⁶¹ and their potential use as a drug delivery vehicle for lipophilic molecules. Specifically, the cationic hexanuclear metalla-prism $[(p\text{-cymene})_6\text{Ru}_6(\text{tpt})_2(\text{dhbq})_3]^{6+}$ (tpt = 2,4,6-trispyridyl-1,3,5-triazine; dhbq = 2,5-dihydroxy-1,4-benzoquinonato) was synthesized and used to encapsulate the hydrophobic Pt(II) complex $[\text{Pt}(\text{acac})_2]$ (acac = acetylacetonato) (Figure 6).⁶⁰ The metalla-prism is water soluble and is moderately cytotoxic (IC_{50} of ca. 23 μM) against human ovarian A2780 cancer cells, while the $[\text{Pt}(\text{acac})_2]$ is completely inactive. Interestingly, the encapsulated Pt(acac)₂ ($[\text{Pt}(\text{acac})_2] \subset [(p\text{-cymene})_6\text{Ru}_6(\text{tpt})_2(\text{dhbq})_3]^{6+}$), was 20-fold more cytotoxic (IC_{50} ca. 1 μM) than the metalla-prism. This initial study provided the proof-of-concept for

what Therrien defined as “the Trojan horse strategy” of hiding a cytotoxic agent in the cavity of a metallacage until, after internalisation within the diseased cells, the drug can be released and perform its cell-killing act.

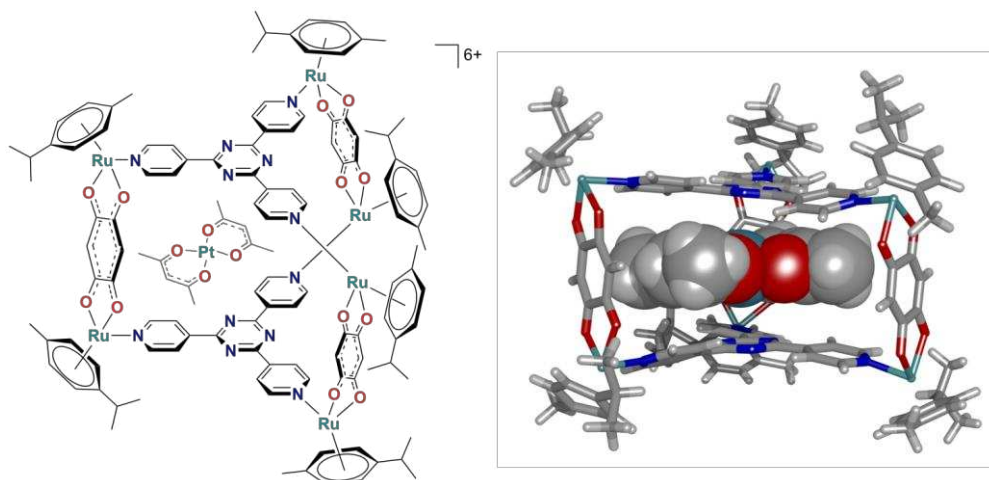


Figure 6. Ruthenium(II)-based host-guest system, $\text{Pt}(\text{acac})_2 \cdot [(\text{p-cymene})_6\text{Ru}_6(\text{tpt})_2(\text{dhbq})_3]^{6+}$ adapted from reference⁶⁰ (CCDC n° 673229). The X-Ray structure was obtained from CCDC (n° 673229) and modified accordingly using Discovery Studio software.

Subsequently, a hexaruthenium metallacage of the type $[\text{Ru}_6(\text{p-}i\text{PrC}_6\text{H}_4\text{Me})_6(\text{tpt})_2(\text{C}_6\text{H}_2\text{O}_4)_3]^{6+}$ (tpt = 2,4,6-tris(pyridin-4-yl)-1,3,5-triazine) was investigated for the release mechanism of encapsulated fluorescent pyrene derivatives and for anticancer properties *in vitro*.⁵⁰ Interestingly, the fluorescence of the pyrene derivatives is quenched upon encapsulation, allowing for the release of the molecule to be monitored by fluorescence spectroscopy. The initial experiments determined that there was no release of the guest molecule at pH 2 or pH 7 as the obtained fluorescent spectrum showed significant quenching of the pyrene group, while guest release occurred at pH 12.⁵⁰ Concerning the antiproliferative properties, IC_{50} values for the free pyrene derivative, the hexaruthenium complex and the encapsulated pyrene within the hexaruthenium complex were reported. The results showed that, while the free pyrene derivative and the cage complex alone were scarcely cytotoxic ($\text{IC}_{50} > 20 \mu\text{M}$ and $16 \pm 2.3 \mu\text{M}$, respectively), the host-guest complex was considerably more active ($6 \pm 0.8 \mu\text{M}$).⁵⁰ Fluorescence microscopy data suggested that the increased cytotoxicity was due to an increased uptake of the poorly soluble pyrene derivative into the cancer cell after being delivered by the water-soluble ruthenium cage complex. However, further studies would be necessary to clarify the mechanisms of intracellular release of the pyrene molecule, and the possible synergic anticancer effects of the cage-pyrene system.

The same group studied the encapsulation properties of the hexaruthenium metallacage with a series of functionalised fluorescent pyrene derivatives using NMR (^1H , 2D, DOSY) spectroscopy and electrospray ionization mass spectrometry (ESI-MS).⁶² The synthesis of the host-guest system proceeded *via* a two-step process: first the di-ruthenium half sandwich molecular “clip” reacts with silver triflate to produce a reactive intermediate; afterwards, a 2:1 solution of the tridentate (2,4,6-tris(pyridin-4-yl)-1,3,5-triazine) and the pyrene derivative is introduced to form

the host-guest complex *via* self-assembly.⁶² The antiproliferative properties of the vacant cage and the pyrene-cage complexes were investigated in human A2780 ovarian cancer cells. According to the obtained results, the vacant cage had a moderate antiproliferative effect, while the encapsulated complexes resulted in lower IC₅₀ values.⁶² Two of the guest complexes, two pyrene derivatives tethered to either a carbonic anhydrase inhibitor or to a glutathione transferase inhibitor, respectively, showed antiproliferative effects comparable to cisplatin. The results also showed that the hexaruthenium cage complexes can help improve the efficacy of the insoluble inhibitors and can successfully deliver them into cells *in vitro*.

Therrien and co-workers developed further the host-guest properties of their drug delivery system by carrying out experiments to determine the effects of the portal size of the ruthenium half-sandwich complex on the retention of the planar [Pd(acac)₂] complex and the pyrene derivative 1-(4,6-dichloro-1,3,5-triazin-2-yl)pyrene used as guest molecules.⁶³ Thus, three hexaruthenium cages were prepared by extending the polycyclic aromatic system in the di-ruthenium bridging ligands, using the 1,4-naphthoquinonato, 1,4-anthraquinonato, and 5,12-naphthacenedionato analogues, resulting in the decrease of the portal size while the internal cavity remained largely the same. Using ¹H NMR to monitor the chemical shift of the protons on the cage complex, a 1:1 stoichiometry of the cage complex to the encapsulated molecule was estimated. Fluorescence studies were carried out to determine the release of the pyrene derivative from the cage complexes. As expected, the results showed a trend for the smaller pore size retaining the guest molecule more effectively. Moreover, the ability of the hosts to deliver guests into cancer cells was evaluated and the uptake mechanism studied by ICP-MS and fluorescence microscopy.⁶³ Overall, the rate of intracellular release of the guest molecule was found to depend on the portal size of the host. Nevertheless, all cages delivered the guest to similar intracellular organelles and the mechanisms of uptake involved endocytosis/macropinocytosis rather than passive diffusion across the cell membrane.⁶³

Although hexaruthenium metallocages have seen most investigation as a future supramolecular coordination drug delivery system so far due to their highly desirable water solubility, a number of other SCCs have undergone preliminary drug encapsulation and pharmacological studies *in vitro*, to assess their potential as drug delivery systems. For example, surface functionalized porous coordination nanocages of Cu(II) and 5-(prop-2-ynyloxy)isophthalic acid (pi) bearing polymer (PEG5k) material have successfully been synthesized using a “Click chemistry” approach.⁶⁴ The scaffold is composed of 12 di-copper paddlewheel clusters and 24 isophthalate moieties, with 8 triangular and 6 square windows that are roughly 8 and 12 Å across, respectively. The internal cavity has a diameter of ca. 15 Å and the cage has high stability in aqueous medium. In addition, the cages’ drug load and release capacity has been evaluated using the anticancer drug 5-fluorouracil (5-FU).⁶⁴ Drug release experiments were carried out by dialyzing the drug-loaded Cu(pi)-PEG5k against buffer solution (PBS, pH 7.4) at room temperature. Interestingly, around 20% of the loaded drug was released during the first 2 hours, while a flatter

release curve can be observed up to 24 hours. The latter slow release has been associated to the slow diffusion rate of 5-FU caused by the strong interaction between Lewis acid sites in Cu(pi) and base site in 5-FU.

Concerning other Cu(II)-based scaffolds, the system based on the stepwise assembly of the metal–organic framework [Cu₂₄(5-NH₂-isophthalate)₂₄(bipyridine)₆(H₂O)₁₂] derived from the [Cu₂₄(5-NH₂-isophthalate)₂₄] cuboctahedron was also synthesized, composed by two kinds of cages (namely, 6 micropores and 1 mesopore).⁶⁵ Similarly to the above mentioned study, drug release experiments were carried out by dialysis of the 5-FU loaded in the MOF in PBS buffer solution (pH 7.4) at 37 °C.⁶⁵ Thus, ca. 80% of the loaded drug was released during the initial fast-release (7.5 h), likely to be due to the overall degradation of the MOF structure. Then, a much flatter release curve generates up to 24 hours, which was again attributed to the strong interaction between Lewis acid sites in the cage structures forming the MOF and the base site in 5-FU.

Within the M₂L₄ family, Crowley *et al.* have designed a cationic Pd₂L₄ cage using (2,6-bis(pyridin-3-ylethynyl)pyridine) as the bidentate ligand,²⁷ based on previous work by Fujita *et al.*⁶⁶ and Steel *et al.*,⁶⁷ and characterised it using ¹H NMR, ESI-MS and X-ray diffraction (XRD) to show that a quadruple stranded cage with the internal cavity lined up with the nitrogen atom from the central pyridine of the ligand. Interestingly, for the first time, the encapsulation of the anticancer drug cisplatin within the cages' cavity was demonstrated by XRD studies. Moreover, ¹H NMR studies showed the peak corresponding to the internal proton had broadened and shifted downfield, indicative of hydrogen bonding interactions of the host-guest system. The release of cisplatin was facilitated by the introduction of competing ligands (4-Dimethylaminopyridine or Cl⁻) to disassemble the cage, as shown *via* ¹H NMR and ESI-MS. The water solubility and the stability under physiological conditions are both crucial for the biological application of metalla-assemblies. Unfortunately, Pd₂L₄ cages of this type are scarcely soluble in aqueous environment, despite their overall positive charge, and implementation of their hydrophilic character is necessary for example *via* the introduction of water soluble moieties in their scaffold. As an example, PEGylation of Pd₂L₄ systems has shown to efficiently improve the stability of single nanocages in solution.⁶⁸

Recently, Lippard *et al.* synthesized a cationic host–guest complex by reaction of an adamantly Pt(IV) prodrug with an hexanuclear Pt(II) cage in a 4:1 ratio in D₂O with sonication, followed by heating at 80 °C.⁶⁹ The hydrophobic adamantyl moiety of the prodrug molecule is postulated to be encapsulated within the hydrophobic cavity of the hexanuclear cage, as suggested by 1D and 2D NMR spectroscopy. This drug delivery system encapsulating the Pt(IV) complex showed micromolar potency against a small panel of human cancer cell lines (A549, A2780, and A2780CP70) and exhibited higher cytotoxicity (IC₅₀= 14.7 ± 2.8 μM) than the Pt(IV) prodrug and the hexanuclear Pt(II) cage (IC₅₀= 22.3 ± 1.8 μM and 57.7 ± 9.2 μM, respectively).⁶⁹ The cytotoxic effect of the host-guest system is attributed to intracellular release of cisplatin, a conclusion supported by observation of effects characteristic of cisplatin-induced damage in cells. The mechanistic hypothesis is that the Pt(IV) complex is

reduced intracellularly by ascorbic acid thus releasing cisplatin, 1-adamantylamine and succinic acid, as suggested by NMR spectroscopy and mass spectrometry methods.

Following these promising results, Casini *et al.* have recently developed a range of fluorescent *exo*-functionalised Pd₂L₄ metallacages and studied the encapsulation of cisplatin by NMR spectroscopy,⁷⁰ reporting similar downfield shifts for the protons lining the cages internal cavity, as reported previously by Crowley *et al.* for similar systems.²⁷ Most importantly, the cages were shown to be able to encapsulate up to two molecules of the anticancer drug cisplatin by XRD (Figure 7). Thus, the cytotoxicity of the palladium cages and precursor compounds were tested against a panel of human cancer cells, including A549, SKOV-3, and HepG2 cell lines, *in vitro*. Furthermore, the activity of encapsulated cisplatin in the benzyl alcohol-derived palladium cage was evaluated against SKOV-3 cancer cells in comparison to cisplatin. Interestingly, the encapsulated cisplatin showed an important decreased IC₅₀ value ($1.9 \pm 0.5 \mu\text{M}$) compared to free cisplatin ($15.4 \pm 2.2 \mu\text{M}$) and the vacant cage complex ($11.6 \pm 1.7 \mu\text{M}$), respectively.⁷¹ Notably, the reported metallacages were non-toxic in healthy rat liver tissue *ex vivo*. Furthermore, the Pd(II) metallacages showed fluorescence properties due to the used ligand system and fluorescence microscopy studies allowed to study their uptake in cancer cell lines.

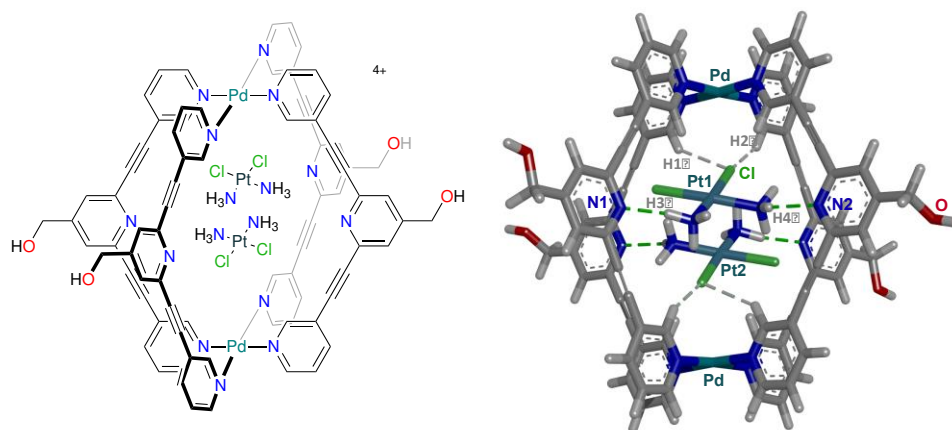


Figure 7. Scheme and X-ray structure of the Pd₂L₄ metallacage encapsulating two cisplatin molecules (H1-Cl: 2.786 Å; H2-Cl: 2.328 Å; N1-H3: 2.181 Å; N2-H4: 2.326 Å; Pt1-Pt2: 3.439 Å). The X-Ray structure was obtained from CCDC (n° 1431657) and modified accordingly using Discovery Studio software.⁷⁰

Selective accumulation of metallacages in tumours has been hypothesized to occur *via* the enhanced permeability and retention (EPR) effect,⁷² which has been widely explored in cancer therapy for delivery *via* passive targeting.⁷³ In fact, the EPR effect targeting solid tumours has been predominantly shown to be involved in the passive targeting of drugs with a molecular weight of more than 40 kDa (20–200 nm in diameter) and for low molecular weight drugs presented in drug-carriers such as polymeric conjugates, liposomes, polymeric nanoparticles, as well as for micellar systems.⁷⁴ However, for supramolecular metallacages, with molecular weight of ca. 2-3 kDa and diameter of ca. 10 Å, the EPR effect is not likely to influence their delivery. Furthermore,

numerous studies evidence that the extent of the EPR effect also varies significantly between patients.⁷³ Therefore, it can be assumed that successful conjugation of cell-specific ligands to the outside of the metallacage, including tumour-targeting peptides (TTPs) that are specific for tumour related surface markers such as membrane receptors,^{56,75} could improve its target specificity and efficacy. However, this concept has been scarcely explored so far. For example, one study has showed non-covalent peptide coating on self-assembled $M_{12}L_{24}$ coordination spheres,⁷⁶ while encapsulation of a protein within a $Pd_{12}L_{14}$ cage (L = bidentate ligand) has been achieved by appropriate *endo*-functionalization of the ligands.⁷⁷ In this case, ligands were first tethered to the protein. Afterwards, following the addition of metal ions and other ligands, coordination nanocages self-assembled around the protein. The latter was the first example of encapsulation of a protein within synthetic host molecules and may reveal novel strategies to delivery of proteins at specific site and to control their function.

With the aim of implementing supramolecular metallacages as drug delivery systems, the first example of bioconjugation of self-assembled Pd_2L_4 cages to a model linear peptide was recently reported.⁷⁸ In this case, the approach of bioconjugation of metallocages was based on amide bond formation between the carboxylic acid (or amine) serving as *exo*-functionalized ligand/cage and the amine (or carboxylic acid) groups of the model peptide side chains. Thus, the bioconjugation was performed using two different approaches: i) direct tethering of the metallacage to the peptide (Approach I); or ii) initial anchoring of the ligand to the peptide, followed by metallacage self-assembly (Approach II) (Figure 8).⁷⁸ Formation of the metallacage-peptide constructs was assessed *via* high-resolution ESI-MS, also coupled to high performance liquid chromatography (LC-MS). So far the best results were achieved with Approach II, where first the coupling of the peptide to the ligands constituting the cages was performed, followed by *in situ* reconstitution of the Pd_2L_4 cages *via* self-assembly. The obtained results open the possibility of efficient bioconjugation of metallacages to peptides which could be extended to targeting moieties such as peptides or affimers, and possibly also to antibodies.

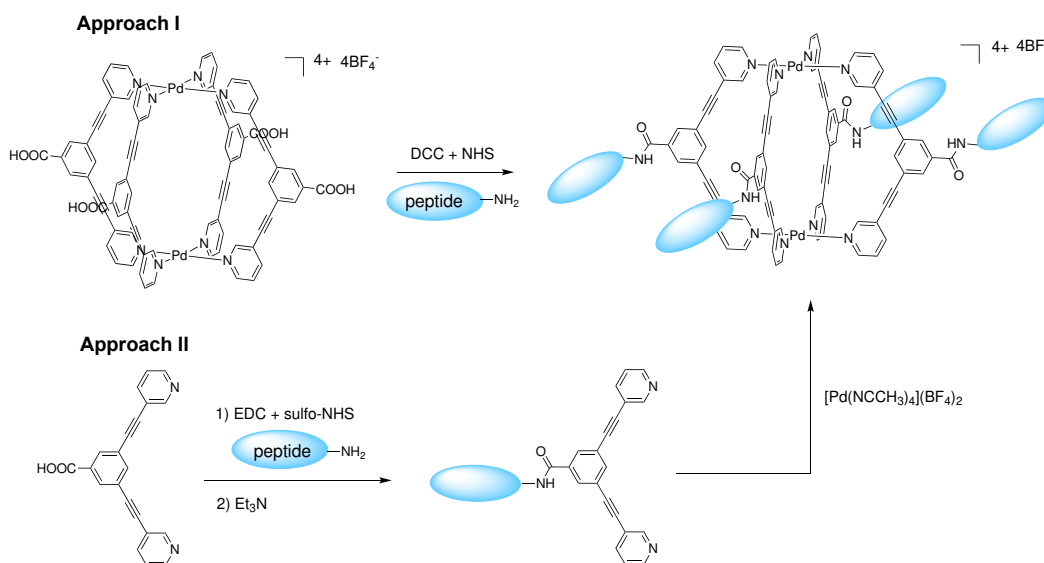


Figure 8. Scheme of the two different bioconjugation approaches applied to conjugate a Pd₂L₄ cage to a model peptide *via* amide bond formation: (i) direct tethering of the metallacage to the peptide (Approach I); or (ii) initial anchoring of the ligand to the peptide, followed by metallacage self-assembly *in situ* (Approach II).⁷⁸ Theoretically, both approaches can produce bioconjugated Pd₂L₄ cages tethered to four peptide units.

Fluorescent metallacages would be a highly desirable drug delivery system, since their fluorescence would allow to track their cellular distribution *in vitro*, and thus, provide insight into their mechanisms of cellular accumulation. However, quenched photoluminescence of Pd₂L₄ metallacage systems is often observed, which can be attributed to two primary factors: *i*) the so-called “heavy metal effect” observed upon self-assembly of luminescent ligands to the metal ion nodes,⁷⁹ and *ii*) the disruption of the emissive conjugated system. Therefore, in order to improve the fluorescence properties of Pd₂L₄ cages (L = fluorescent bispyridyl ligand), Casini and Kühn *et al.* have synthesized cages *exo*-functionalised *via* amide bond with either naphthalenyl or anthracenyl moieties.⁷⁹ The cages were also investigated for their anticancer properties in human lung and ovarian cancer cell lines *in vitro*. While the observed cytotoxic effects hold promise and the cages resulted to be more effective than cisplatin in both cell lines, surprisingly, it was observed that the emission properties were extremely scarce (quantum yields even below 1%). To explain this unexpected observation, time dependant density functional theory (TD-DFT) experiments were carried out on the anthracenyl-based ligand and revealed that the cause of the observed quenching was most likely due to a lower probability for HOMO to LUMO excitation (2%) than the corresponding carboxyl functionalised ligands (24%).⁷⁹ Further studies were carried out to determine the possible emission wavelength of the ligands by converting the calculated energy difference between the excitation energy and the relaxation energy, and converting this to a wavelength which was found to be in the IR region ($\lambda_{\text{max}} = 2000 \text{ nm}$), whereas the carboxyl and amine functionalised ligands emitted in the visible range ($\lambda_{\text{max}} = 420 \text{ nm}$). From this observation two reasons were given for the poor fluorescence of the ligands. Firstly, the probability of a HOMO-LUMO excitation is much smaller for the anthracenyl-based ligand. Secondly, the energy differences between the highest excited state and the non-relaxed ground level did not correlate to a wavelength within the visible range.⁷⁹

In order to avoid disruption of the emissive conjugated fluorescent tag, the direct conjugation of highly luminescent ruthenium based fluorophores to the Pd₂L₄ metallacage scaffold *via* an unsaturated linker group (such as an amide or cycloazide) was attempted.⁸⁰ Thus, the highly luminescent fluorophore tris(bipyridine)ruthenium was conjugated to the Pd₂L₄ metallacage *via* a saturated alkyl spacer. The hypothesis proved accurate as, remarkably, the resulting cage resulted to be amongst the most emissive metallacages known to date ($\Phi_{\text{(cage)}} = 66\%$).⁸⁰

The control of the properties of the cavity defined by the SCC is another essential feature to implement them as drug delivery systems. For example, in contrast to the previously mentioned metallacages, anthracene-based Pt(II)- and Pd(II)-linked coordination capsules provide a characteristic spherical cavity closely surrounded

by polyaromatic frameworks. The isolated cavity features a diameter of ca. 1 nm and a volume of ca. 600 Å³. These systems can accommodate various neutral molecules in the confined cavity through hydrophobic interactions, but also π -stacking, in aqueous solution. Cages of this type were recently reported to be able to encapsulate fluorescent pyrene, as well as caffeine molecules,^{55,81} while fluorescence microscopy studies evidenced the high extracellular stability of these systems.⁸¹ However, the cytotoxic effects of the capsules – without and with their guest molecules – were very pronounced against different types of cancer cell lines, which may prevent their applications as pure drug delivery systems.

4. Helicates as DNA/ RNA recognition domains

Nucleic acids are exciting biomolecular targets because they offer the potential to regulate information transfer at an early stage, before the genetic code is translated into proteins. Metal complexes that bind to DNA have been highly explored for several years, with the cationic charge that metals impart being attractive for recognition of the polyanionic nucleic acid structures.^{82,83} Examples include complexes that coordinate to the bases, intercalate, or bind to the phosphate backbone of regular duplex DNA or, more recently, that recognize less common DNA structures such as bulges, quadruplexes or junctions.^{84–87} Such complexes have been explored as therapeutic drugs, fluorescent imaging agents, footprinting agents⁸⁸ and for nanotechnology applications.^{89,90}

With respect to SCCs, the field has been pioneered by Hannon and co-workers with the synthesis *via* self-assembly of metallocsupramolecular cylinders composed by bis(pyridylimine) ligands bound to metal ions. Thus, for example, dinuclear Fe(II) metallocsupramolecular triple helicates [Fe₂L₃]Cl₄ (L = C₂₅H₂₀N₄, Figure 9) were shown to specifically recognize various unusual DNA or RNA structures,⁹¹ such as Y-shaped three-way junctions,^{91–93} three-way junctions containing unpaired nucleotides, the so-called T-shaped three-way junctions,⁸² while other groups also studied binding to human telomeric G-quadruplex (G4) DNA.⁹⁴ Interestingly, these helicates can also bind nucleic acids bulges containing two or more unpaired nucleotides.⁹⁵ Concerning other first row transition metals, di-nickel helicates exhibited chiral selective binding with human telomeric G4, the right-handed helix selectively stabilizing antiparallel G-quadruplex, whilst the left-handed compound did not, and both enantiomers stabilized hybrid G4s.⁹⁴ Following these promising results, water-stable iron helices, synthesized directly *via* diastereoselective self-assembly, could discriminate human telomeric hybrid G4 structures with high chiral selectivity.⁹⁶ It is worth mentioning that G-quadruplexes are non-canonical DNA structures formed by guanine (G)-rich sequences that can self-associate into stacks of G-quartets linked by loop nucleotides. G4s are of growing interest in chemistry and biology, largely due to their peculiar and diverse molecular structures, which include parallel and antiparallel topologies. Recently, G4s have been reported to have critical regulatory roles in biological processes, including but not limited to DNA replication, transcription, and translation, providing new and important

mechanisms for controlling gene expression and genome stability, as well as novel targets in cancer chemotherapy.⁹⁷ Thus, the possibility of chiral recognition of G4 structures by helicates may pave the way to their selective targeting for gene modulation and anticancer effects.

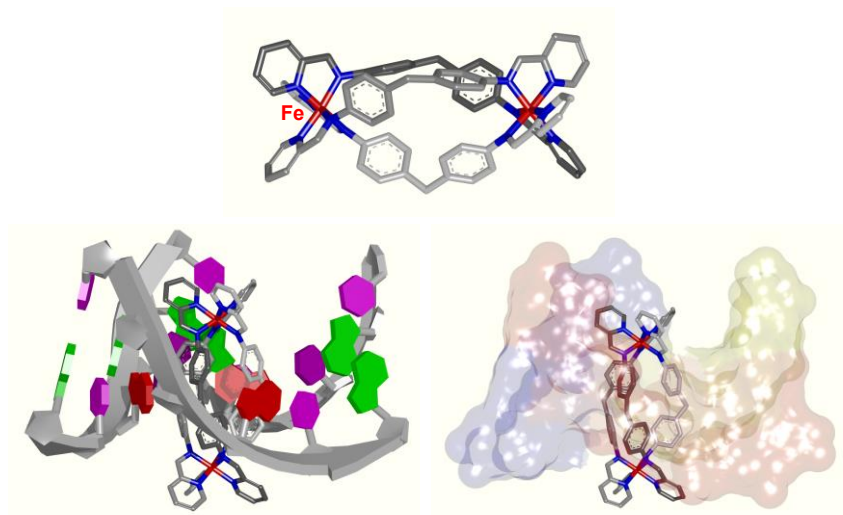


Figure 9. Structure a cylindrical di-iron(II) complex, [Fe₂L₃]⁴⁺ (L=C₂₅H₂₀N₄) and its binding to the central cavity of an RNA three-way junction. Reproduced from reference.⁹¹ The structures were obtained from PDB (accession code 4JIY) and modified accordingly using Discovery Studio software.

Recently, Scott *et al.* developed a new strategy whereby the absolute configurations of individual metal centres are controlled and linked together to form the prototype helicate-like architectures not relying on the use of rigid ligands. In this case the key has been the development of simple self-assembling, optically pure monometallic complexes utilizing amino acid derivatives as the source of chirality.⁹⁸ These complexes were connected together with linear linkers to form helical bimetallic species known as ‘flexicates’.⁹⁸ The compounds are readily water-soluble and remarkably stable in a variety of media. Interestingly, some of these flexicates have shown antibacterial properties, as well as good activity against a range of cancer cell lines.^{98,99} Interestingly, two triple-helical dinuclear iron supramolecular complexes were also shown to act as chiral inhibitors of amyloid- β aggregation, as demonstrated using fluorescent cell-based screening and multiple biophysical and biochemical approaches.¹⁰⁰

More recent studies by Hannon and Brabec *et al.* have shown that iron(II) supramolecular helicates inhibit the interaction of the HIV-1 transactivator protein Tat with TAR (transactivation responsive region) RNA, playing a critical role in HIV-1 transcription.¹⁰¹ Specifically, the authors reported on the interactions of M- and P-enantiomers of [Fe₂L₃]Cl₄ with the TAR RNA by using thermal denaturation, electrophoretic mobility shift assay, and RNase A footprinting. The obtained results show that both M- and P-[Fe₂L₃]Cl₄ bind with high affinity to the TAR RNA and discriminate this three-base bulge containing RNA against fully matched RNA duplex, constituting robust templates for further developing TAR ligands with improved efficiency and selectivity and with potential for HIV therapies.

It is evident that future research in the discovery and development of helicates should be directed towards structure-activity relationships to achieve a more rational drug design of therapeutic supramolecular compounds with respect to the targeting of specific DNA secondary structures. Furthermore, such molecules may be also developed as chemical probes to aid in uncovering the functions of these unconventional nucleic acid structures in cancer biology, particularly if endowed with luminescent properties. However, for helicates to be capable of translation to the clinic a number of criteria need still to be addressed, including optical purity and stability, solubility and chemical stability in water, availability on a practical scale, and synthetic diversity.

5. Conclusions and future outlook

Discrete supramolecular constructs attract strong research interest because of their myriad applications. In this context, 3D supramolecular coordination complexes constitute a promising research area, particularly for pharmaceutical and chemosensory application in biological systems. In fact, 3D SCCs can be designed to fine-tune the dimensions of the cavity, its hydrophobicity and H-bonding properties, as well as to adjust to the influence of the solvent in driving the molecular recognition. Moreover, the interplay between the metal and ligand precursors sometimes endows the final constructs with unique properties that are not present in the individual components. Furthermore, introduction of various functionalities into the chemical composition of the cage can provide a platform for targeted drug delivery, as highlighted in this Viewpoint, or for biochemical applications including imaging of specific biomolecules. For example, chiral helicates can recognize specific DNA structures, while DNA-coated nanospherical cages may be envisaged as biological sensors in DNA/RNA detection, gene regulation and biological screening. A schematic representation of the possible areas of bio-related applications for SCCs is presented in Figure 10.

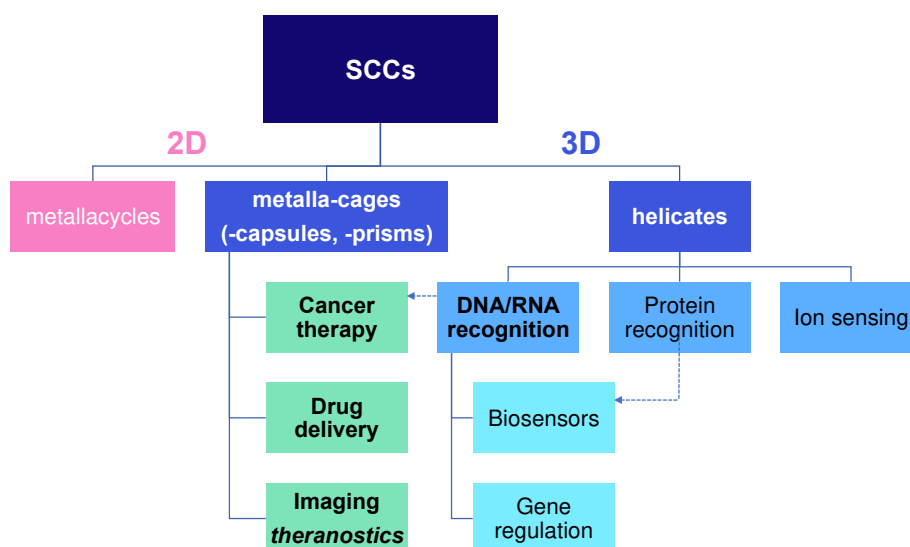


Figure 10. Schematic representation of the various types of SCCs and the scope of their biological applications. In bold font are the topics discussed in this Viewpoint.

Overall, in this vibrant research field, several challenges can be identified. For example, attaining a selective and spatially controlled release of guest molecules with metallacages remains a difficult task. To this aim, introduction of stimuli-responsive building blocks within the metalla-assembly is required. Different stimuli can potentially be employed to provoke guest release at specific sites (e.g. tumour tissues): pH, temperature, redox reactions, polarity, light or electric field. Recently, Clever and co-workers have synthesised a Pd-based metallacage including light-responsive dithienylethene (DTE) spacers.¹⁰² After appropriate irradiation, a geometrical change in the DTE ligands occurs, altering the size of the cavity, thus forcing the initially encapsulated $[B_{12}F_{12}]^{2-}$ guest molecule to remain outside. An example of redox active metallacage composed of an extended tetrathiafulvalene-based ligand and a *cis*-blocked Pd^{2+} complex was synthesized and characterized by Salle *et al.*¹⁰³ Remarkably, this electron-rich cage can be disassembled upon chemical oxidation with the thianthrenium radical cation, and subsequently reassembled by reduction with tetrakis(dimethylamino)ethylene. From the same group, a proof-of-concept related to the redox-control of the binding/releasing process in a host-guest system has been achieved by designing a neutral and robust redox-active metallacage involving two extended-tetrathiafulvalene ligands bound to four Pt(II) organometallic complexes.¹⁰⁴ When neutral, the cage can encapsulate a planar polyaromatic guest (coronene). Remarkably, the chemical or electrochemical oxidation of the host-guest complex causes the reversible expulsion of the guest outside the cavity, illustrating the key role of counter-anions along the exchange process.

Another synthetic challenge concerns the possibility to encapsulate different drug molecules in the same supramolecular metallacage. Notably, multicavity metallosupramolecular architectures have the potential to allow the binding of multiple different guests within a single assembly and could open up new applications to achieve combination therapy of different cytotoxic agents.¹⁰⁵ For example, interlocked coordination metallacages, or metal-mediated dimers, have only been reported recently, the first example of which was reported by the Fujita group in 1999.¹⁰⁶ The formation of interlocked metallacage dimers can be difficult to predict, however the judicious choice of a suitable guest template has been shown to form stable interlocked metallacages, as has the use of complimentary ligands that will stabilise each other through intramolecular forces, for example π -stacking interactions.¹⁰⁷ Currently, the applications for the mechanically interlocked complexes have been postulated to be in molecular machinery and small molecule recognition, owing to the different cavity environments interlocked cages possess, however new applications in drug delivery of multiple therapeutic agents may be envisioned as the field progresses.

Concerning other possible developments, 3D SCCs may also be optimized for implementing imaging modalities in biological systems. Challenges in this area not only include achieving a size- or shape-selective

dynamic molecular recognition, but also include detecting and amplifying guest-bonding events to produce a measurable output. Accordingly, an easy-to-measure signal and a proper communication system must be included in the overall molecular design. A representative example of this application was recently reported by Duan *et al.* where a hexanuclear gadolinium octahedral nanocage was self-assembled as an efficient multimeric magnetic resonance probe for selectively responding glucosamine.¹⁰⁸ In the supramolecular scaffold, six Gd³⁺ ions were strongly bound to the four planar ligands. The rigid facial bridging ligands provided additional enhancements for the proton relaxivity around gadolinium ions, ensuring the application of magnetic resonance imaging (MRI) *in vivo*. Another promising example for bioimaging applications is, in our view, the one reported by Oppel *et al.* on the preparation of acylhydrazones of 2,3-dihydroxybenzaldehyde, which act as ligands for the self-assembly of heterodinuclear lanthanide(III)-gallium(III) helicates.¹⁰⁹ The new ligands are substituted at the acylhydrazone unit which binds the lanthanide ion, providing further possibilities for the synthesis of heteronuclear scaffolds and for helicates functionalization with more sophisticated substituents (e.g. peptides).

At the frontier of supramolecular chemistry for biomedical applications, a *theranostic* system with the capability to perform dual functions (*i.e.* imaging and therapy) by unifying self-assembly, coordination chemistry, and supramolecular chemistry, has recently been developed by Stang and co-workers.¹¹⁰ In detail, coordination-driven self-assembly of a tetragonal Pt-based prismatic metallacage incorporating aggregation-induced emission (AIE) luminogens was achieved. The metallacage was then encapsulated within spherical micelles formed from a mixture of mPEG-DSPE (DSPE: 1,2-distearoyl-phosphatidyl-ethanolamine) and biotin-PEG-DSPE, wherein the presence of polyethylene glycol and biotin groups provided a means to stabilize the prisms sitting safely within the hydrophobic pocket. These theranostic nanoparticles were shown to actively target the biotin receptor-positive cancer cells selectively over biotin receptor-negative cells. *In vivo* studies demonstrated that the nano-cage system possesses higher antitumor efficacy with lower toxicity compared with free platinum anticancer drugs.¹¹⁰

Finally, to move forward in this fascinating research area, bioinorganic chemists should also demonstrate the possibility to control the *speciation* of SCCs in physiological environment in order to avoid possible side effects. Thus, we should be able to address the difference between the toxicity related to the “naked”, non-coordinated metal ion, and that of the corresponding metal stabilized by the coordinating ligands. To this aim, the investigation of the stability of SCCs in aqueous environment and of their reactivity with biomolecules should be conducted at the earliest stages of the research, benefiting from the knowledge already available on bioactive metal complexes and related investigational methods. To fine-tune the reactivity of the supramolecular systems and to guarantee a certain stability, the integration of organometallic moieties within the SCCs may be a valuable strategy. For example, recently, a number of studies exploited N-heterocyclic carbene (NHC) systems to obtain 3D cage compounds.^{111,112} Thus, Pöthig *et al.* reported on the first [2]rotaxane featuring a functional organometallic Ag(I)

NHC scaffold.¹¹³ Interestingly, the organometallic interlocked system can reversibly and quantitatively be switched to an organic [3]rotaxane *via* a unique pH-dependent (de-)coordination of the involved metal ions.

Concerning drug delivery applications, the study of the drug encapsulation properties of SCCs in physiological-type conditions should be implemented with techniques other than NMR spectroscopy, for which relatively high concentrations of the host-guest system are necessary, such as fluorescence spectroscopy and Isothermal Titration Calorimetry (ITC). In any case, the toxicity of such metal-based entities should be carefully evaluated in various appropriate investigational models, including *in vitro* (e.g. cell cultures), but also *ex vivo* (e.g. tissue slices), and, eventually, *in vivo*, also taking advantage of recent high-resolution biophysical and analytical techniques aimed at the detection of metal ions in biological samples. Overall, we hope that this Viewpoint will encourage further developments in this exciting interdisciplinary research field and that more input will come from the bioinorganic and medicinal inorganic chemistry communities. Please enjoy and get inspired!

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Metal-mediated self-assembly of supramolecular coordination complexes (SCCs) has been explored, among other areas of potential usage, for biological applications. In fact, SSCs featuring 3D structures hold great promise and have been found to interact with DNA, possess anticancer activity, and function as drug-delivery vectors. This Viewpoint provides an overview of the 3D SCCs structures most suitable for future biomedical applications and defines the challenges in this vibrant and interdisciplinary research field.

